

**REMARKS**

The Advisory Action of December 31, 2002, relates to the examination of claims 20-41. Claims 22, 25, 29, 33, and 36 are canceled. Claims 20, 23, 27, 31, and 34 are amended. No new matter is inserted into the application.

***Advisory Action***

In the Advisory Action, the Examiner states that the Reply after Final filed on December 13, 2002 has been entered into the record and considered, but does not place the application into condition for allowance.

The rejections precluding allowance of the application are (1) the rejection of claims 20-25, 27-29 and 31-41 under 35 U.S.C. § 103(a) for allegedly being obvious over Huse '762 in view of Gelfand '292, and (2) the rejection of claims 26 and 30 under 35 U.S.C. § 103(a) for allegedly being obvious over Huse '762 in view of Gelfand '292, and further in view of Dodge '117. Applicants will address these rejections in turn below. First, however, Applicants address the Examiner's remarks made in the Advisory Action.

On page 2 of the Advisory Action, the Examiner asserts that the arguments in the Reply attack the references individually

instead of the combination of references. Applicants respectfully disagree with the Examiner. The Examiner fails to answer Applicants' arguments that the references could not be combined by one of ordinary skill in the art, such as on page 5 of the Reply after Final filed on December 13, 2002.

Further, the Examiner asserts that the features relied upon in the arguments (i.e., (a) reactions are not in the presence of two or more different kinds of nucleotides, and (b) nucleotides of the claimed invention are nucleotides which are not modified at the 2' position of the ribose sugar) are not recited in the rejected claim(s).

The Examiner's first assertion, that is, that the claims do not recite that the reactions are in the presence of two or more different kinds of nucleotides, is clearly erroneous. The claims recite "in the presence of two or more kinds of nucleotide analogs...." For example, see claim 20, lines 10-11.

Regarding the Examiner's assertion that the claims do not recite that unconventional nucleotides are excluded, Applicants have amended the claims to recite that at least one of nucleotide analogs is selected from the group consisting of 7-Deaza-dGTP, 7-Deaza-dATP, dITP, and hydroxymethyl dUTP. For example, see claim 20, lines 6-7. Support for this amendment is

found in canceled claims 22, 25, 29, 33, and 36. Since the Examiner has already searched and considered these limitations, the amendments to claims 20, 23, 27, 31, and 34 do not raise new issues or require further search and/or consideration.

***Rejections under 35 U.S.C. § 103***

*Huse '726 in view of Gelfand '292 (Paragraph 3 of the Office Action)*

Claims 20-25, 27-29 and 31-41 stand rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Huse '762 (USP 5,681,726) in view of Gelfand '292 (USP 5,939,292). Claims 22, 25, 29, 33, and 36 are canceled, thus rendering rejection of these claims moot. Applicants respectfully traverse the rejection applied to the pending claims. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Huse '726 discloses a method for amplifying a DNA fragment containing a nucleotide analog via PCR. Huse '726 fails to disclose a method for amplifying DNA in the presence of two or more kinds of nucleotide analogs, wherein there is a uniform incorporation of these nucleotide analogs into a targeted nucleic acid during amplification. The Examiner attempts to

make up for the deficiencies of Huse '726 by combining therewith the disclosure of Gelfand '292. However, the hypothetical combination of Gelfand '292 and Huse '726 still fails to render the present invention obvious.

In Gelfand '292, the definition of the term "unconventional (nucleotide)" is different from that of the present invention. Namely, in column 4, lines 30-39, c7dGTP and dITP, which are used in the present invention, are exemplified as conventional nucleotides. In addition, Gelfand '292 discloses in column 6, lines 1-7, that unconventional nucleotides include rNTPs in which the 2' position of the ribose sugar is modified in comparison with dNTPs, ribonucleotide analog containing substitutions at the 2' position (such as 2'-fluoro or 2'-amino), and ribonucleotide analog termination in which normal hydroxyl at the 3' position is replaced with a hydrogen. Therefore, the "nucleotide analog" of the present invention is completely different from the "unconventional nucleotide" of Gelfand '292.

Accordingly, since neither Gelfand '292 nor Huse '726 disclose that one of the nucleotide analogs is selected from the group consisting of 7-Deaza-dGTP, 7-Deaza-dATP, dITP, and hydroxymethyl dUTP, all of the claimed elements of the present

invention are not met. For these reasons, the rejection is improper and should be withdrawn.

Rejection over Huse '726 in view of Gelfand '292 and further in view of Dodge '117 (Paragraph 4 of the Office Action)

The Examiner rejects claims 26 and 30 under 35 U.S.C. § 103(a) for allegedly being obvious over Huse '762 in view of Gelfand '292, and further in view of Dodge '117 (USP 5,912,117). Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

The Examiner relies on Dodge '117 to teach a compound for lowering  $T_m$  value. However, the hypothetical combination of these references still does not make the present invention obvious since none of the references disclose that one of the nucleotide analogs is selected from the group consisting of 7-Deaza-dGTP, 7-Deaza-dATP, dITP, and hydroxymethyl dUTP. For this reason, the rejection under 35 U.S.C. § 103 is improper and should be formally withdrawn.

**Conclusion**

In summary, all of the present claims define patentable subject matter such that this application should be placed into condition for allowance. Early and favorable action on the merits of the present application is thereby requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. No. 45,702) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), the Applicants hereby petition for an extension of two (2) months to Sunday, February 16, 2003, in which to file a reply to the Office Action. The required fee of \$410.00 is enclosed herewith.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any

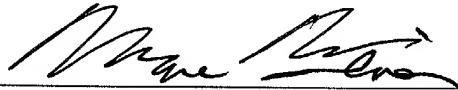
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additional fees required under 37 C.F.R. §1.16 or under 37 C.F.R. §1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachment: Version with markings showing changes made



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VERSION WITH MARKINGS SHOWING CHANGES MADE

In the claims:

Claims 22, 25, 29, 33, and 36 are canceled.

Claims 20, 23, 27, 31, and 34 are amended as follows:

20. (Twice Amended) A method for amplifying a DNA, comprising the steps of

(a) preparing a cDNA comprising at least one of nucleotide analogs by a reverse transcription reaction using an RNA as a template in the presence of the at least one of nucleotide analogs selected from the group consisting of 7-Deaza-dGTP, 7-Deaza-dATP, dITP, and hydroxymethyl dUTP [using an RNA as a template]; and

(b) amplifying a desired DNA from the cDNA obtained in the above step (a), in the presence of two or more kinds of nucleotide analogs, wherein at least one nucleotide analog is selected from the group consisting of 7-Deaza-dGTP and dITP, [incorporated in the amplifying step in place of dGTP or dCTP] and at least one nucleotide analog is selected from the group consisting of 7-Deaza-dATP and hydroxymethyl dUTP [incorporated in the amplifying step in place of dATP or dTTP], wherein the



nucleotide analogs are uniformly incorporated into the resulting DNA [and do not cause termination of the amplification], thereby selectively amplifying DNA of a target sequence derived from RNA.

23. (Twice Amended) A method for amplifying a DNA, comprising the steps of:

(a) providing a template DNA comprising a nucleotide analog selected from the group consisting of 7-Deaza-dGTP, 7-Deaza-dATP, dITP, and hydroxymethyl dUTP; and

(b) amplifying a desired DNA from the template DNA of step (a) in the presence of the following substances (i) to (iii):

(i) at least one nucleotide analog selected from the group consisting of 7-Deaza-dGTP and dITP [to be incorporated in the amplifying step in place of dGTP or dCTP],

(ii) at least one nucleotide analog selected from the group consisting of 7-Deaza-dATP and hydroxymethyl dUTP [to be incorporated in the amplifying step in place of dATP or dTTP], and

(iii) a compound for lowering the  $T_m$  value of a double-stranded nucleic acid,

wherein the nucleotide analogs (i) and (ii) are uniformly incorporated into the resulting DNA [and do not cause termination of the amplification].

27. (Twice Amended) A method for amplifying a DNA comprising the steps of:

(a) preparing a cDNA by a reverse transcription reaction using RNA as a template in the presence of at least one nucleotide analog selected from the group consisting of 7-Deaza-dGTP, 7-Deaza-dATP, dITP, and hydroxymethyl dUTP [using RNA as a template]; and

(b) amplifying a desired DNA from the cDNA of the above step (a) in the presence of the following substances (i) to (iii):

(i) at least one nucleotide analog selected from the group consisting of 7-Deaza-dGTP and dITP [to be incorporated in the amplifying step in place of dGTP or dCTP],

(ii) at least one nucleotide analog selected from the group consisting of 7-Deaza-dATP and hydroxymethyl dUTP [to be incorporated in the amplifying step in place of dATP or dTTP], and

(iii) a compound for lowering the  $T_m$  value of a double-stranded nucleic acid, wherein the nucleotide analogs (i) and

(ii) are uniformly incorporated into the resulting DNA [and do not cause termination of the amplification],  
thereby selectively amplifying DNA of a target sequence derived from RNA.

31. (Twice Amended) A kit for amplifying a DNA in the presence of two or more kinds of nucleotide analogs [a nucleotide analog] by the use of a DNA fragment comprising at least one nucleotide analog selected from the group consisting of 7-Deaza-dGTP, 7-Deaza-dATP, dITP, and hydroxymethyl dUTP as a template, comprising two or more kinds of nucleotide analogs, wherein the two or more nucleotide analogs are:

(i) at least one nucleotide analog selected from the group consisting of 7-Deaza-dGTP and dITP [to be incorporated in place of dGTP or dCTP], and

(ii) at least one nucleotide analog selected from the group consisting of 7-Deaza-dATP and hydroxymethyl dUTP [to be incorporated in place of dATP or dTTP, and

wherein the nucleotide analogs do not cause termination of the DNA amplification].

34. (Twice Amended) A kit for amplifying a DNA in the presence of two or more kinds of [at least one] nucleotide analogs [analog] by the use of a template DNA fragment comprising at least one nucleotide [analogs] analog selected from the group consisting of 7-Deaza-dGTP, 7-Deaza-dATP, dITP, and hydroxymethyl dUTP, comprising two or more kinds of nucleotide analogs and a compound for lowering the  $T_m$  value of a double-stranded nucleic acid,

wherein the two or more kinds of nucleotide analogs are:

(i) at least one nucleotide analog selected from the group consisting of 7-Deaza-dGTP and dITP [to be incorporated in place of dGTP or dCTP], and

(ii) at least one nucleotide analog selected from the group consisting of 7-Deaza-dATP and hydroxymethyl dUTP [to be incorporated in place of dATP or dTTP, and

wherein the nucleotide analogs do not cause termination of the DNA amplification].